Treatment Effect of Ergocalciferol on Bone Metabolism Indexes and Parathyroid Hormone in Hemodialysis Patients

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Introduction. Vitamin D deficiency is a common problem in end-stage renal disease patients under hemodialysis. Both active and nutritional vitamin D supplementation have been recommended for its treatment. In this study we aimed to evaluate the effects of treatment with ergocalciferol on bone metabolism indexes in hemodialysis patients.

Materials and Methods. In a randomized controlled trial, 40 hemodialysis patients were randomly allocated to the intervention (n = 20) and placebo (n = 20) groups. During the study, 4 patients in the placebo and 1 in the intervention group were excluded. Patients received calcitriol, 0.25 mg/d, with ergocalciferol, 50 000 IU, or placebo weekly for 3 months. Serum levels of 25-hydroxyvitamin D, calcium, parathyroid hormone, and alkaline phosphatase were measured before and after treatment.

Results. 25-hydroxyvitamin D levels were significantly improved in the intervention group (12.00 ± 4.90 ng/mL versus 29.89 ± 9.48 ng/mL, $P < .001$), but the placebo group had no improvement (14.23 ± 7.62 ng/mL versus 13.87 ± 8.04 ng/mL, $P > .05$). There was no significant changes in serum calcium, parathyroid hormone, or alkaline phosphatase levels in each group. Eight patients (42.1%) in the intervention compared to zero cases in the placebo group had normal 25-hydroxyvitamin D levels after treatment ($P = .004$). No cases of hypercalcemia were seen in the studied patients.

Conclusions. Treatment with ergocalciferol could significantly improve vitamin D deficiency with no significant effects of serum calcium or parathyroid hormone levels.

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INTRODUCTION

Vitamin D deficiency or insufficiency is a common problem in chronic kidney disease (CKD) with a prevalence of more than 90% in CKD and end-stage renal disease (ESRD) patients.[1-4] Low levels of vitamin D is associated with high bone turnover, secondary hyperparathyroidism, and decreased bone mineral density, muscle weakness, anemia, resistance to treatment with recombinant human erythropoietin, and increased mortality in ESRD patients.[1-5]

Different mechanism have been suggested for vitamin D insufficiency in CKD including inadequate nutritional intake, decreased sunlight exposure, proteinuric loss and decreased hepatic synthesis of 25-hydroxyvitamin D, and increased expression of human vitamin D 24-hydroxylase gene, the cytochrome P-450 enzyme that specifically catabolizes vitamin D and its metabolites.[6-8] Adequate production of 1,25-hydroxyvitamin D by renal and extrarenal 1α-hydroxylase requires sufficient 25-hydroxyvitamin D supply. With

progressive kidney function impairment, there is a decrease in 1,25-dihydroxycholecalciferol production with subsequent hypocalcemia, secondary hyperparathyroidism, and metabolic bone disease.[9,10]

Active vitamin D analogs are accepted treatments to prevent or treat the secondary hyperparathyroidism and mineral disorders among patients with ESRD. However, the Kidney Disease Improving Global Outcome initiative recommendation is to use nutritional vitamin D along with active forms to correct vitamin D deficiency in ESRD patients.[11] This recommendation is due to the fact that the 1-α-hydroxylase enzyme remains active in the extrarenal tissues of ESRD patients, which is important for local tissue function.[12]

Nutritional inactivated vitamin D (cholecalciferol or ergocalciferol) has been shown to successfully increase serum vitamin D levels, reduce parathyroid hormone (PTH) levels with no risk of hypercalcemia or hyperphosphatemia in ESRD patients.[13-16] However, the exact effects of nutritional vitamin D is not yet understood. In this study, we aimed to evaluate the effects of treatment with ergocalciferol on bone metabolism indexes in hemodialysis patients.

MATERIALS AND METHODS

In a randomized controlled trial, 40 ESRD patients under hemodialysis for more than 3 months during 2017 were recruited. All ESRD patients aged between 20 and 70 years old with vitamin D deficiency and a PTH level greater than 300 pg/mL, serum calcium level between 8.4 mg/dL and 10 mg/dL, and serum phosphorus level between 2 mg/dL and 5 mg/dL were included. All of the patients were on routine hemodialysis 3 to 4 times a week at Bu-Ali Hospital, Ardabil, Iran. Exclusion criteria were malignancy, death, kidney transplantation, or change in mode of dialysis during the study period. The ethics committee of Ardabil University of Medical Sciences approved the study and all patients provided informed consent.

The patients were randomly assigned to receive ergocalciferol, 50000 units (intervention group, n = 20), or placebo (n = 2 0), weekly, and calcitriol, 0.25 mg/d, for 3 months. Placebo was prepared with the same size, color, and shape. All of the patients were instructed to use their routine treatments during the study and not to restrict their everyday diet. Patients' adherence to medication were evaluated in each visit. The patients and the physician evaluating the outcome of the treatments were blinded to the group allocation. The drug was given to patients by the hemodialysis nurse every week during the dialysis session.

Serum levels of 25-hydroxyvitamin D, calcium, PTH, and alkaline phosphatase were measured before and at the end of the study. Patients' demographic findings and laboratory findings were recorded and compared between the two groups.

All data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL, USA). Results were expressed as mean ± standard deviation or percentage. Continuous data were analyzed using the independent *t* test or the Mann-Whitney U test, as applicable. The categorical parameters were compared using the chi-square test or the Fisher exact test. The paired samples *t* test was used to evaluate the changes before and after treatment. *P* values less than .05 were considered significant.

RESULTS

During the study, 4 patients were excluded from the placebo group (3 died and 1 switched to peritoneal dialysis), and 1 patient from the intervention group had kidney transplantation and was excluded. Final analysis was performed with 19 patients in the intervention and 16 patients in the placebo group. The patients were comparable regarding the baseline findings (Table 1). Most of the patients were male in both groups with diabetic nephropathy as the main cause of ESRD.

Table 2 demonstrates laboratory findings before

Table 1. Baseline Characteristics of Study Groups

Characteristics	Intervention Group (n = 19)	Placebo Group (n = 16)
Age, y	51.70 ± 12.39	51.82 ± 10.16
Sex		
Male	13 (68.4)	13 (81.3)
Female	6 (31.6)	3 (18.8)
Dialysis duration, y	4.55 ± 1.08	4.02 ± 1.87
Cause of kidney failure		
Diabetes mellitus	10 (52.6)	7 (43.8)
Glomerulopathy	3 (15.8)	4 (25)
Tubular nephritis	2 (10.5)	2 (12.5)
Unknown	4 (21.1)	3 (18.8)

Table 2. Laboratory Findings Before and After Intervention

Serum Parameters	Intervention Group (n = 19)	Placebo Group (n = 16)	*P*
Vitamin D, ng/mL			
Before	12.00 ± 4.90	14.23 ± 7.62	.28
After	29.89 ± 9.48	13.87 ± 8.04	< .001
Percentage of change	184.52 ± 131.17	3.97 ± 26.05	< .001
Calcium, mg/dL			
Before	7.99 ± 0.87	8.07 ± 0.63	.75
After	8.15 ± 0.84	8.19 ± 1.08	.91
Percentage of change	2.45 ± 7.59	1.45 ± 9.40	.73
Parathyroid hormone, pg/mL			
Before	593.95 ± 212.83	390.47 ± 225.33	.008
After	518.52 ± 335.55	487.50 ± 484.39	.82
Percentage of change	-7.63 ± 47.66	39.48 ± 132.80	.08
Alkaline phosphatase, mg/dL			
Before	298.50 ± 182.22	264.94 ± 89.11	.49
After	310.15 ± 223.14	279.75 ± 79.43	.60
Percentage of change	11.87 ± 31.17	14.86 ± 26.61	.76

and after intervention and their percentage of change between the groups. Vitamin D levels were comparable between the two groups before intervention, while there was significantly higher levels of 25-hydroxyvitamin D in the intervention group compared to the placebo group after the study. Although PTH levels were significantly higher in the intervention group before the study, there was no significant difference after intervention. Serum PTH levels were decreased in the intervention group, while it was increased in the placebo group, with no difference in the percentage of change between the two groups.

The only within-group significant change was in 25-hydroxyvitamin D levels among the patient in the intervention group ($P < .001$).

Only 8 patients, all in the intervention group (42.1%), significantly improved to normal vitamin D ranges after treatment ($P = .004$). No cases of hypercalcemia were seen in neither of the groups.

DISCUSSION

In this study, we observed that vitamin D levels were significantly increased following treatment with ergocalciferol and calcitriol compared to those treated with calcitriol alone with no significant effect on calcium, PTH, and alkaline phosphatase. Studies have demonstrated that vitamin D have endocrine as well as paracrine and autocrine functions which yield to different pathophysiological effects.[17,18] Most CKD and ESRD patients have low vitamin D levels, which should be treated properly. It is still unclear whether to treat vitamin D deficiency with active or nutritional vitamin D. Sufficient levels of 25-hydroxyvitamin D is necessary to provide proper extrarenal calcitriol production for paracrine actions. Also, the need for active vitamin D is increased with a decrease in GFR and disease progression to ESRD. Using nutritional and activated vitamin D together seems to have synergistic effects on both the classic and nonclassic actions.[8,19.]

In our study, 42% of patients treated with a combination of ergocalciferol and calcitriol reached normal vitamin D levels. Similarly, Bhan and coleagues[16] observed a significant increase in 25-hydroxyvitamin D levels with weekly or monthly ergocalciferol, 50 000 IU. In their study, 90% of the patients achieved vitamin D sufficiency. Marckmann and colleagues[20] found a significant increase in vitamin D levels in the treatment with cholecalciferol, 40 000 U/wk, compared to the control group. In a long-term treatment period of a mean of 39.2 weeks, Assimon and coworkers[21] observed a higher serum 25-hydroxyvitamin D levels in the ergocalciferol group undergoing maintenance hemodialysis.

Moe and colleagues[22] have noted that treatment with a daily dosage of 4000 IU/d of cholecalciferol for 1 month with 2000 IU for 2 additional months was sufficient to increase vitamin D levels above 37 ng/mL and to normalize serum calcitriol in CKD stage 3 and 4.

We observed no episodes of hypercalcemia during the study period in our patients. We also

found no significant change in calcium and alkaline phosphatase in the intervention and placebo groups. Hewitt and colleagues[15] also found no hypercalcemia or hyperphosphatemia following treatment with cholecalciferol 50 000 IU weekly for 8 weeks. Other studies have shown that ergocalciferol has negligible effects on serum calcium and phosphorus.[23-25] It could be concluded that treatment with nutritional vitamin D (ergocalciferol and cholecalciferol) along with active vitamin D effectively increase 25-hydroxyvitamin D levels without increasing the risk of hypercalcemia or hyperphosphatemia. One possible explanation for the lack of calcemic effect could be that weekly nutritional vitamin D supplementation had no effect on intestinal absorption of calcium.[26]

Studies have indicated that PTH levels following treatment with active or nutritional vitamin D is significantly decreased in predialysis patients and lower CKD stages, but not in ESRD patients under hemodialysis.[13] Marckmann and colleagues[20] also reported that although there was significant decrease in PTH levels in predialysis patients, but no significant changes was seen in hemodialysis patients. Following treatment with ergocalciferol, we observed a decrease in PTH levels, but an increase in PTH levels in placebo group; however, these changes were not significant. Previous clinical trials have also reported no effects of nutritional vitamin D on PTH in hemodialysis patients.[15,16,27-31] Considering all these studies, it seems that nutritional vitamin D has no effect on PTH in patients on hemodialysis.

One study has recommended that insufficient dosages given cannot achieve proper level to decrease PTH.[32] Thus, the proper dosage of nutritional vitamin D, either ergocalciferol or cholecalciferol, should be properly defined in ESDR patients under hemodialysis. We used the KDOQI guidelines of an oral weekly doses of 50 000 IU of ergocalciferol for 12 weeks for mild to severe deficiency to correct vitamin D deficiency. However, with this protocol, only 42% of patients reached sufficient levels. Thus, higher doses may be needed to reach better responses.

We evaluated the changes in 25-hydroxyvitamin D levels, as in our center we are unable to measure 25-hydroxyvitamin D2 levels and so could not define the exact effect of ergocalciferol on this measurement. Other limitation of this study are small sample size and shorter follow-up duration.

CONCLUSIONS

In conclusion, treatment with ergocalciferol could significantly improve vitamin D deficiency with no significant effects of calcium and PTH levels.

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CONFLICT OF INTEREST

None declared.

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